Hypoxic preconditioning of mesenchymal stromal cells induces metabolic changes, enhances survival, and promotes cell retention in vivo.

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Public Summary:
Mesenchymal stem cells/multipotent stromal cells (MSCs) are promising therapeutics for a variety of conditions. However, after transplantation, cell retention remains extremely challenging. Given that many hypoxic signals are transitory and that the therapeutic administration of MSCs is typically into tissues that are normally hypoxic, we studied the effect of hypoxic preconditioning (HP) prior to new exposure to hypoxia. We show that preincubation for 2 days or more in 1% oxygen reduces serum deprivation-mediated cell death, as observed by higher cell numbers and lower incorporation of EthD-III and Annexin V. Consistently, HP-MSCs expressed significantly lower levels of cytochrome c and heme oxygenase 1 as compared to controls. Most importantly, HP-MSCs showed enhanced survival in vivo after intramuscular injection into immune deficient NOD/SCID-IL2Rgamma(-/-) mice. Interestingly, HP-MSCs consume glucose and secrete lactate at a slower rate than controls, possibly promoting cell survival, as glucose remains available to the cells for longer periods of time. In addition, we compared the metabolome of HP-MSCs to controls, before and after hypoxia and serum deprivation, and identified several possible mediators for HP-mediated cell survival. Overall, our findings suggest that preincubation of MSCs for 2 days or more in hypoxia induces metabolic changes that yield higher retention after transplantation.

Scientific Abstract:
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